Published in final edited form as:
Liver Transpl. 2007 January ; 13(1): 122–129. doi:10.1002/lt.20995.

Outcomes in Hepatitis C Virus–Infected Recipients of Living Donor vs. Deceased Donor Liver Transplantation

Norah A. Terrault[1], **Mitchell L. Shiffman**[2], **Anna S.F. Lok**[3], **Sammy Saab**[4], **Lan Tong**[5], **Robert S. B Jr.**[6], **Gregory T. Everson**[7], **K. Rajender Reddy**[8], **Jeffrey H. Fair**[9], **Laura M. Kulik**[10], **Timothy L. Pruett**[11], **Leonard B. Seeff**[12], and **the A2ALL Study Group**

[1]Department of Medicine, Division of Gastroenterology, University of California at San Francisco, San Francisco, CA

[2]Department of Medicine, Division of Gastroenterology, Virginia Commonwealth University Medical Center, Richmond, VA

[3]Department of Internal Medicine, University of Michigan, Ann Arbor, MI

[4]Department of Medicine, University of California, Los Angeles, Los Angeles, CA

[5]Department of Surgery, University of Michigan, Ann Arbor, MI

[6]Department of Medicine, Columbia University Medical Center, New York, NY

[7]Department of Medicine, Division of Gastroenterology, University of Colorado, Denver, CO

[8]Department of Medicine, Division of Gastroenteology, University of Pennsylvania, Philadelphia, PA

[9]Department of Surgery, University of North Carolina, Chapel Hill, NC

[10]Department of Medicine, Division of Gastroenterology, Northwestern University, Chicago, IL

[11]Department of Surgery, University of Virginia, Charlottesville, VA

[12]National Instutes of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD

Abstract

In this retrospective study of hepatitis C virus (HCV)–infected transplant recipients in the 9-center Adult to Adult Living Donor Liver Transplantation Cohort Study, graft and patient survival and the development of advanced fibrosis were compared among 181 living donor liver transplant (LDLT) recipients and 94 deceased donor liver transplant (DDLT) recipients. Overall 3-year graft and patient survival were 68% and 74% in LDLT, and 80% and 82% in DDLT, respectively. Graft survival, but not patient survival, was significantly lower for LDLT compared to DDLT ($P = 0.04$ and $P = 0.20$, respectively). Further analyses demonstrated lower graft and patient survival among the first 20 LDLT cases at each center (LDLT ≤20) compared to later cases (LDLT > 20; $P =$

Address reprint requests to A2ALL Study, Data Coordinating Center, 315 W. Huron St., Suite 240, Ann Arbor, MI 48103-4262. Telephone: 734-998-6580; FAX: 734-998-6620; o2all-dcc@umich.edu.

Presented in part at the American Association for the Study of Liver Diseases, 56th Annual Meeting, San Francisco, CA, November 11-15, 2005.

Publication number 2 of the Adult-to-Adult Living Donor Liver Transplantation Cohort Study.

Supplemental data have been supplied by the University Renal Research and Education Association as the contractor for the Scientific Registry of Transplant Recipients. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the Scientific Registry of Transplant Recipients or the U.S. government.

0.002 and $P = 0.002$, respectively) and DDLT recipients ($P < 0.001$ and $P = 0.008$, respectively). Graft and patient survival in LDLT >20 and DDLT were not significantly different ($P = 0.66$ and $P = 0.74$, respectively). Overall, 3-year graft survival for DDLT, LDLT >20, and LDLT ≤20 were 80%, 79% and 55%, with similar results conditional on survival to 90 days (84%, 87% and 68%, respectively). Predictors of graft loss beyond 90 days included LDLT ≤20 vs. DDLT (hazard ratio [HR] = 2.1, $P = 0.04$), pretransplant hepatocellular carcinoma (HCC) (HR = 2.21, $P = 0.03$) and model for end-stage liver disease (MELD) at transplantation (HR = 1.24, $P = 0.04$). In conclusion, 3-year graft and patient survival in HCV-infected recipients of DDLT and LDLT >20 were not significantly different. Important predictors of graft loss in HCV-infected patients were limited LDLT experience, pretransplant HCC, and higher MELD at transplantation.

Hepatitis C virus (HCV)–related end-stage liver disease is the leading indication for liver transplantation in the United States. Adult-to-adult living donor liver transplantation represents an important means of expanding the donor pool, making transplantation available to an increasing number of patients on the waiting list. Prior reports of HCV-infected living donor liver transplant (LDLT) recipients having a poorer graft outcome than HCV-infected deceased donor liver transplant (DDLT) recipients have raised concerns regarding this donor option for HCV-infected persons.[1-5] In a study of 764 LDLT and 1,470 matched DDLT recipients transplanted between 1998 and 2001, the overall risk of graft failure was 60% higher in LDLT recipients compared to DDLT recipients (hazard ratio [HR] = 1.6; 95% confidence interval, 1.1, 2.5) after adjusting for baseline differences in the groups such as serum creatinine, United Network for Organ Sharing medical urgency status, and need for life support.[4] In HCV-positive patients, a similar pattern was seen of significantly lower graft survival in LDLT compared with DDLT recipients. In contrast, a second study from the United Network for Organ Sharing database found no significant difference in the 2-year graft survival between 279 LDLT and 3,955 DDLT recipients transplanted between 1999 and 2002 with a diagnosis of chronic HCV ($P = 0.21$).[5]

Several theories have been proposed to explain differences in HCV recurrence in LDLT vs. DDLT recipients. The rapid liver regeneration occurring in the early posttransplant period in recipients of living donor grafts may alter early virologic or immunologic events and thereby affect the risk of progressive liver disease. Also, live donor recipients are more likely than deceased donor recipients to share human leukocyte antigens and although the relationship between human leukocyte antigens matching and risk of recurrent HCV is controversial, it represents another difference between LDLT recipients and DDLT recipients that may affect HCV disease recurrence. Alternatively, because LDLT donors typically are younger and the ischemia times are shorter than with DDLT donors, outcomes may be better among recipients of LDLT than of DDLT. At the present time, these proposed mechanisms for an altered natural history of HCV infection in recipients of LDLT vs. DDLT remain speculative.

The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) is a consortium of 9 U.S. liver transplant centers performing adult-to-adult LDLT with the primary goal of examining outcomes of adult-to-adult LDLT vs. DDLT. Both retrospective and prospective studies are ongoing, aimed at garnering information on donor and recipient outcomes of LDLT over the decade from 1998 to 2008. In the present study, the retrospective A2ALL cohort was used to compare graft and patient survival and the risk of advanced fibrosis in HCV-infected recipients who underwent either LDLT or DDLT.

PATIENTS AND METHODS

Study Population

The A2ALL retrospective cohort includes 819 adult patients who had a potential living donor evaluated between January 1, 1998 and February 28, 2003. Inclusion required that a patient's potential donor undergo an initial history and physical examination. HCV infection was defined by serologic and virologic tests available prior to transplantation. Among these potential recipients, 382 had HCV infection. Excluding the HCV patients who never went to the operating room for transplantation (n = 94), those who went to the operating room but whose transplant procedure was aborted (n = 8), those who received deceased donor split liver transplantation (n = 4), and those who received a domino liver transplant (n = 1), we studied the 275 HCV patients who received either a LDLT or a whole DDLT. Patients with hepatocellular carcinoma (HCC) were included. The HCV patients who received a LDLT were compared to those who received a whole DDLT.

Data were abstracted from the clinical records at each site. For specific variables, including date of death, information from the Scientific Registry of Transplant Recipients was used to augment data available in A2ALL. Immunosuppression protocols, indications for liver biopsy, treatment of rejection, and treatment of recurrent HCV infection were not standardized across centers. Virological data were incomplete and therefore not used in the analyses. HCV genotypes were available for 57% of patients; HCV RNA measurements were available for 59% prior to transplantation. The laboratory model for end-stage liver disease (MELD) score was calculated at the time of transplantation, and values were capped at 40.[6] Cold ischemia time was defined as the interval from the donor cross-clamp to graft removal from ice. Acute rejection was defined by the requirement for antirejection treatment whether or not rejection was biopsy proven. Biliary complications included leaks and strictures identified by operative, endoscopic, or radiological studies.

The primary study endpoint was graft survival, and all causes of graft loss were included; death was regarded as a graft loss. Since graft loss within the first 90 days after transplantation was unlikely to be secondary to HCV, both overall graft survival and graft survival beyond 90 days were considered. Additionally, prior A2ALL analyses of graft survival for all indications found that the risk of graft failure was strongly associated with the number of previous LDLTs performed at a given center. Examination of this effect by 5-case increments found that the first 20 LDLT cases at a center had an increased risk of graft loss, compared to cases beyond the first 20.[7] Thus, graft survival among the first 20 LDLT cases at each center (LDLT ≤20) was compared with later cases (LDLT >20).

Secondary endpoints included patient survival and liver biopsy evidence of HCV disease. Liver histology was assessed by a single pathologist at each center using a standardized scoring system. Pathologists were blinded to patient outcomes. The modified Knodell hepatitis activity index was used to measure necroinflammatory activity,[8] and the Ishak score was used to assess fibrosis.[9] Biopsies lacking Knodell and Ishak scores and those occurring more than 2 weeks after the start of treatment for HCV were excluded. "Advanced" histological disease was defined as an Ishak fibrosis score greater than or equal to 3. In analyses of the time to advanced disease, biopsies occurring less than 30 days after transplant and those without Ishak score available were excluded.

The study was approved by the Institutional Review Boards and Privacy Boards of each of the 9 participating transplant centers and the University of Michigan Data Coordinating Center.

Statistical Analysis

Descriptive statistics included median, mean, standard error, and range as appropriate. Comparisons of recipient characteristics, donor characteristics, immunosuppression, and posttransplant complications between LDLT and DDLT recipients were performed using chi-square tests for categorical variables and 2-sample *t* tests for continuous variables. Graft and patient survival were estimated by the Kaplan-Meier method, and unadjusted comparisons were made using the log-rank test. The study sample size provides 90% power to detect an HR ≥2.0 (for LDLT compared to DDLT) for either graft or patient survival, assuming a 2-sided log-rank test with alpha = 0.05. Cox regression was used to adjust for the effects of potentially confounding variables. The predictor variable of primary interest was donor type (LDLT vs. DDLT). Overall graft survival and survival limited to grafts surviving beyond the first 90 days posttransplantation were considered. Additionally, graft survival among the first 20 LDLT cases at each center (LDLT ≤20) was compared with later cases (LDLT >20). Other potential confounders tested in the Cox regression models were recipient age, recipient gender, recipient race/ethnicity, donor age, donor gender, year of transplantation (before or during 2000 vs. after 2000), presence of HCC, pretransplant MELD score, cold ischemia time, initial use of tacrolimus, and initial use of mycophenolate mofetil. In addition, the following variables were entered and tested in the Cox model as time-varying covariates: prednisone use at 3 months posttransplantation, treated acute rejection, acute rejection requiring antibody therapy, antiviral therapy, and biliary complications. The interaction between immunosuppression and acute rejection was evaluated.

We estimated the probability of Ishak score ≥3 by the Kaplan-Meier method, and we tested for a difference between LDLT and DDLT using a log-rank test, although biopsy data were inconsistently collected. Biopsies occurring more than 2 weeks after start of treatment for HCV were censored at that time. All analyses were performed using SAS/STAT 9.1 User's Guide (SAS Publishing, Cary, NC).

RESULTS

A total of 275 patients in the A2ALL Retrospective Cohort Study had HCV infection and underwent liver transplantation, 181 having received an LDLT and 94 having received a DDLT. The median follow-up posttransplantation was 3.25 years (3.66 in LDLT and 2.78 in DDLT recipients). Two-thirds (65.5%) of patients were transplanted prior to institution of MELD-based DDLT allocation (76.8% of LDLT and 43.6% of DDLT, $P < 0.0001$). The majority of transplant recipients were Caucasian (91%), 68% were male, and the median age of the cohort was 51.1 years. HCC was present in 23% of the patients. The baseline characteristics of the DDLT and LDLT recipients are shown in Table 1. The laboratory MELD score at the time of transplantation, the proportion of male donors, and the cold ischemia times were significantly higher in DDLT recipients than in LDLT recipients. DDLT recipients were older, had older donors, and were more likely to have hepatocellular carcinoma than LDLT recipients, but these differences were not statistically significant. Of those patients with HCC, 47.6% had tumors within Milan criteria (a single lesion ≤5 cm in diameter, or no more than 3 lesions ≤3 cm in diameter) and 52.4% (61.1% of LDLT and 40.7% of DDLT) had tumors outside the Milan criteria.

Immunosuppression was similar between DDLT and LDLT recipients. The majority of patients received tacrolimus (76.2% of LDLT recipents and 78.7% of DDLT recipients), mycophenolate mofetil (61.3% of LDLT and 56.4% of DDLT recipients) and prednisone (86.2% of LDLT and 89.4% of DDLT recipients) as baseline immunosuppression. The rate of treated acute rejection was 47.0% of LDLT recipients compared to 37.2% of DDLT recipients ($P = 0.16$), and the median time to first episode of rejection was 14 days among

LDLT recipients with at least 1 rejection, compared to 23 days among DDLT recipients with at least 1 rejection ($P = 0.39$). The use of antibody therapy (OKT3 or thymoglobulin) for treatment of acute rejection was higher in LDLT vs. DDLT recipients (25.9% vs. 11.4% of treated rejection episodes), but this difference was not statistically significant ($P = 0.08$). The frequency of biliary complications was significantly higher in LDLT recipients, occurring in 39.2%, compared to 20.2% of DDLT recipients ($P = 0.0014$).

Graft and Patient Survival

Recipients of LDLT had a significantly lower cumulative graft survival than recipients of DDLT in unadjusted analysis ($P = 0.040$, log-rank test). Cumulative patient survival rates were not significantly different between LDLT and DDLT recipients ($P = 0.20$, log-rank test). The primary causes of graft loss in the LDLT and DDLT recipients are listed in Table 2. Recurrent HCV was the primary or secondary cause of graft loss in 10 (5.5%) of the 181 LDLT recipients and in 2 (2.1%) of the 94 DDLT recipients ($P = 0.19$).

Subsequent analyses, with the LDLT recipients divided into the first 20 patients (LDLT ≤20, n = 78) and subsequent patients (LDLT >20, n = 103) at each center, revealed a significant difference in rates of graft survival between LDLT ≤20 and DDLT ($P = 0.0007$) and between LDLT ≤20 and LDLT >20 ($P = 0.0023$), but not between DDLT and LDLT >20 ($P = 0.66$) (Fig. 1). The cumulative graft survival for DDLT, LDLT >20, and LDLT ≤20 recipients was 87%, 84%, and 72% at 1 year, respectively, and 80%, 79%, and 55% at 3 years, respectively. Similarly cumulative graft survival beyond the first 90 days after transplantation was significantly lower in LDLT ≤20 compared to LDLT >20 ($P = 0.021$) and DDLT ($P = 0.052$), but there was no difference in graft survival between LDLT >20 and DDLT ($P = 0.74$) (Fig. 2). The cumulative survival of grafts that survived beyond the first 90 days for DDLT, LDLT >20, and LDLT ≤20 recipients was 91%, 93%, and 86% at 1 year, respectively, and 84%, 87%, and 68% at 3 years, respectively.

Patient survival in LDLT ≤20 was significantly lower than both LDLT >20 ($P = 0.002$) and DDLT ($P = 0.008$). However, patient survival in LDLT >20 and DDLT were not significantly different ($P = 0.74$). The cumulative patient survival for DDLT, LDLT >20, and LDLT ≤20 recipients was 87%, 91%, and 78% at 1 year, respectively, and 82%, 84% and 63% at 3 years, respectively.

Predictors of Graft and Patient Survival

Factors associated with significantly lower overall graft survival in univariable analysis included LDLT ≤20, older recipient age at transplantation, pretransplant diagnosis of HCC, higher laboratory MELD score at transplantation, the use of antibody therapy for treatment of acute rejection, and lack of tacrolimus use. In multivariable analysis, only recipients of LDLT ≤20, older recipient age, pretransplant diagnosis of HCC, higher laboratory MELD score at transplantation, and rejection requiring antibody as a time-varying covariate were significant independent predictors of lower graft survival (Table 3). For graft survival beyond the first 90 days, only LDLT ≤20, pretransplant HCC, and higher MELD at transplantation were independent predictors of graft loss (Table 3).

Factors associated with significantly lower overall patient survival and patient survival beyond the first 90 days in multivariable analysis, were recipients of LDLT ≤20, pretransplant diagnosis of HCC, and higher laboratory MELD score at transplantation (Table 4). There was no difference in patient survival among HCV patients with HCC within Milan criteria compared to those with HCC outside Milan criteria (HR = 1.15; 95% confidence interval, 0.46, 2.87;$P = 0.76$). Among the 20 patients with HCC who died,

recurrent HCC was the primary cause of death in 4 patients (20%) and recurrent HCV was the primary cause of death in 2 patients (10%).

Among LDLT recipients, graft to body weight ratio was not predictive of graft or patient survival.

Histological Severity of Disease

A total of 138 patients (82 LDLT and 56 DDLT) had at least 1 biopsy that could be evaluated for severity of HCV disease at some point posttransplantation, with a median duration of histological follow-up of 12 months (range, 0.03 to 59 months). The proportion of patients with a biopsy evaluated for HCV disease severity varied from 33% to 95% at the different study sites. Of the 224 patients with a functioning graft at 1 year posttransplantation, 63 (28%; 36 LDLT, 27 DDLT) had liver biopsies available at 1 year ± 4 months that could be evaluated for recurrent HCV disease severity. In patients receiving HCV treatment, histology was assessed using biopsies up to 2 weeks following treatment start. There was no significant difference in the total necroinflammatory ($P = 0.19$) or fibrosis scores ($P = 0.93$) between DDLT and LDLT recipients at 1 year posttransplantation (Table 5).

Treatment of HCV was undertaken in 32% of DDLT and 34% of LDLT ($P = 0.70$). In a time-to-event analysis restricted to the 123 patients with a biopsy at least 30 days posttransplantation and no more than 2 weeks after the initiation of HCV treatment, the time required to progress to an Ishak fibrosis score of ≥3 was not different for LDLT vs. DDLT recipients ($P = 0.87$, unadjusted log-rank test) (Fig. 3).

DISCUSSION

In this multicenter U.S. study, we show that the outcomes of HCV-infected patients with LDLT are not significantly different from DDLT recipients once transplant centers have sufficient experience with LDLT. Prior studies examining the effects of LDLT on HCV outcomes failed to take “experience of the transplant program with LDLT” into account, likely contributing to the divergence in reported outcomes. The reasons for the difference in outcomes of HCV-infected live donor transplant recipients early in a center’s experience vs. later are not completely clear. However, most transplant physicians recognize the unique technical challenges in performing living donor transplants in adults, and several publications attest to the higher rate of graft loss early in the posttransplant period related to vascular problems, biliary complications, and small-for-size syndrome.[10,11] These technical issues have great relevance in the first 90 days posttransplantation. However, the observation that graft survival remains lower in recipients of LDLT ≤20 than in recipients of LDLT >20 or DDLT even beyond that time point suggests that ongoing complications resulting from early events ultimately affect graft longevity. Given the findings in our study, future studies evaluating outcomes in HCV-infected LDLT patients will need to consider the effect of “center experience.”

While recurrent HCV infection is essentially universal following transplantation, the rate of histologic disease progression is quite variable. Multiple factors have been linked with worse histological disease, including donor age, HCV genotype, cold and warm ischemia times, treated acute rejection, cytomegalovirus infection, and pretransplant HCV viral load.[12-15] Whether or not recipients of a living-donor liver transplant have an increased risk of recurrent cirrhosis is a question of great interest. The 2 largest protocol biopsy studies, 1 from the United States and 1 from Spain, reported quite disparate results. In a U.S. study of 23 LDLT and 53 DDLT patients, patient and graft survival was not different, and there was no patient with cirrhosis in either group after a median follow-up of 40 months.[16] In

contrast, in a Spanish study using protocol liver biopsies, cirrhosis or liver decompensation occurred in 44% of LDLT patients compared with 29% of DDLT patients ($P = 0.019$).[2] In the present study, the proportion of LDLT recipients with advanced fibrosis, defined as an Ishak fibrosis score of 3 or greater at 1 year posttransplantation, was 14.3% compared to 11.5% in DDLT ($P = 0.75$). Similarly, the rate of progression to advanced fibrosis was not different between LDLT and DDLT recipients. While supportive of our overall results regarding graft survival, cautious interpretation of the histological data are needed, since protocol biopsies were not used and only 28% of patients had biopsies that could be evaluated for recurrent disease at 1 year posttransplantation. Clearly, prospective studies utilizing protocol liver biopsies to assess disease severity are the optimal means of determining whether there is a difference in disease progression and severity between LDLT and DDLT recipients. This is a primary aim of the prospective A2ALL Cohort Study currently underway.

The incidence of HCC is increasing, reflecting, in part, the increasing number of persons with HCV and cirrhosis.[17] Liver transplantation is the treatment of choice for patients with cirrhosis and small HCCs.[18] In this cohort, nearly a quarter of the liver transplant recipients with HCV infection had HCC as an additional diagnosis. Timely transplantation of patients with limited HCC is critical in maximizing good outcomes and in preventing recurrent HCC. Recently, MELD exception scores for HCC were modified, as data showed that prior prioritization points for HCC were unfairly favoring access to DDLT for these patients. LDLT is also an important option for patients with limited HCC and may allow patients' access to liver transplantation in a time interval shorter than for DDLT, thereby reducing the rate of drop-off from the list due to tumor progression. Alternatively, more rapid access to transplantation in patients with tumors at the limits of current United Network for Organ Sharing criteria may allow patients with more aggressive tumor biology and a higher risk of recurrence to be transplanted when they would otherwise have become noncandidates due to tumor progression if DDLT were utilized. In our study, a pretransplant diagnosis of HCC was an independent predictor of reduced overall patient survival beyond 90 days. This observation may be related to the inclusion of patients with more advanced stages of HCC. We did not find a significant difference in overall risk of death in patients with tumors inside vs. outside of the Milan criteria ($P = 0.76$). However, it is noteworthy that the majority of patients in this cohort were transplanted prior to the routine use of aggressive ablative treatment of HCC in patients on the waiting list for transplantation and prior to the implementation of the MELD HCC exception policy.

There are recognized limitations of this study. As this was a retrospective study, data on virologic aspects of HCV disease, such as genotype and HCV viral load, were inconsistently collected and measured. However, we do not believe this limitation would have biased the results. Most studies indicate that genotype is not predictive of survival,[19-21] and pretransplant HCV viral loads did not influence the decision of whether or not to perform LDLT. Additionally, immunosuppression and treatment of acute rejection were not standardized, and the indications for liver biopsies varied from center to center. These differences in posttransplant management may have contributed to differences in graft outcome. Nevertheless, since LDLT and DDLT recipients came from the same centers, differential bias in immunosuppression and acute rejection strategies by donor type may have been reduced. Finally, the median duration of follow-up was relatively short (~3 years), and differences in graft losses due to recurrent HCV between LDLT >20 and DDLT may become evident with long-term follow-up. However, the strengths of our study are the large number of LDLT recipients evaluated, the inclusion of LDLT from multiple large transplant centers to minimize center-specific biases, and the ability to validate key variables using Scientific Registry of Transplant Recipients data.

In conclusion, this study demonstrates that graft survival is not significantly different for recipients of LDLT compared to DDLT once centers have sufficient experience with LDLT. Thus, HCV-infected patients awaiting transplantation should not be denied LDLT if an appropriate living donor is available.

Acknowledgments

The authors thank the following individuals, who were instrumental in the planning, conduct, and/or care of patients enrolled in this study at each of the participating institutions: Jean C. Emond, Robert S. Brown, Jr., Rudina Odeh-Ramadan, and Taruna Chawla, Columbia University Health Sciences, New York, NY; Michael M.I. Abecassis, Andreas Blei, and Patrice Al-Saden, Northwestern University, Chicago, IL; Abraham Shaked, Kim M. Olthoff, Mary Kaminski, and Mary Shaw, University of Pennsylvania Health System, Philadelphia, PA; James F. Trotter, Igal Kam, Scott Heese, and Carlos Garcia, University of Colorado Health Sciences Center, Denver, CO; Rafik Mark Ghobrial, Ronald W. Busuttil, and Lucy Artinian, University of California Los Angeles, Los Angeles, CA; Chris E. Freise, Norah A. Terrault, and Dulce MacLeod, University of California San Francisco, San Francisco, CA; Robert M. Merion, Douglas R. Armstrong, Margaret Hill-Callahan, Terese Howell, Karen Wisniewski, Lan Tong, and Monique Lowe, University of Michigan Medical Center, Ann Arbor, MI; Jeffrey H. Fair and Carrie A. Nielsen, University of North Carolina, Chapel Hill, NC; Carl L. Berg, Timothy L. Pruett, and Jaye Davis, University of Virginia, Charlottesville, VA; Robert A. Fisher, Mitchell L. Shiffman, Cheryl Rodgers, Ede Fenick, and April Ashworth, Virginia Commonwealth University Health System, Richmond, VA; and James Everhart, Leonard B. Seeff, Patricia R. Robuck, and Jay H. Hoofnagle, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Digestive Diseases and Nutrition, Bethesda, MD.

Supported in part by the National Institutes of Health National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK grant numbers U01-DK62536, U01-DK62444, U01-DK62467, U01-DK62483, U01-DK62484, U01-DK62494, U01-DK62496, U01-DK62498, U01-DK62505, U01-DK62531), the American Society of Transplant Surgeons, and the U.S. Department of Health and Human Services, Health Resources and Services Administration.

Abbreviations

HCV	hepatitis C virus
LDLT	living donor liver transplant
DDLT	deceased donor liver transplant
HR	hazard ratio
A2ALL	Adult-to-Adult Living Donor Liver Transplantation Cohort Study
HCC	hepatocellular carcinoma
MELD	model for end-stage liver disease

REFERENCES

1. Gaglio P, Malireddy S, Levitt B, Lapointe-Rudow D, Lefkowitch J, Kinkhabwala M, et al. Increased risk of cholestatic hepatitis C in recipients of grafts from living versus cadaveric liver donors. Liver Transpl. 2003; 9:1028–1035. [PubMed: 14526396]
2. Garcia-Retortillo M, Forns X, Llovet J, Navasa M, Feliu A, Massaguer A, et al. Hepatitis C recurrence is more severe after living donor compared to cadaveric liver transplantation. Hepatology. 2004; 40:699–707. [PubMed: 15349910]
3. Maluf DG, Stravitz RT, Cotterell AH, Posner MP, Nakatsuka M, Sterling RK, et al. Adult living donor versus deceased donor liver transplantation: a 6-year single center experience. Am J Transplant. 2005; 5:149–156. [PubMed: 15636624]
4. Thuluvath P, Yoo H. Graft and patient survival after adult live donor liver transplantation compared to a matched cohort who received a deceased donor transplantation. Liver Transpl. 2004; 10:1263–1268. [PubMed: 15376301]
5. Russo M, Galanko J, Beavers K, Fried M, Shrestha R. Patient and graft survival in hepatitis C recipients after adult living donor liver transplantation in the United States. Liver Transpl. 2004; 10:340–346. [PubMed: 15004758]

6. Freeman RB Jr, Wiesner RH, Harper A, McDiarmid SV, Lake J, Edwards E, et al. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl. 2002; 8:851–858. [PubMed: 12200791]
7. Olthoff KM, Merion RM, Ghobrial RM, Abecassis MM, Fair JH, Fisher RA, et al. Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL Consortium. Ann Surg. 2005; 242:314–323. [PubMed: 16135918]
8. Knodell RG, Ishak KG, Black WC, Chan TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology. 1981; 5:431. [PubMed: 7308988]
9. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol. 1995; 22:696–699. [PubMed: 7560864]
10. Schemmer P, Mehrabi A, Friess H, Sauer P, Schmidt J, Buchler MW, et al. Living related liver transplantation: the ultimate technique to expand the donor pool? Transplantation. 2005; 80(1 Suppl):S138–141. [PubMed: 16286892]
11. Broelsch CE, Frilling A, Testa G, Cicinnati V, Nadalin S, Paul A, et al. Early and late complications in the recipient of an adult living donor liver. Liver Transpl. 2003; 9(10 Suppl 2):S50–S53. [PubMed: 14528429]
12. Berenguer M, Ferrell L, Watson J, Prieto M, Kim M, Rayon M, et al. HCV-related fibrosis progression following liver transplantation: increase in recent years. J Hepatol. 2000; 32:673–684. [PubMed: 10782918]
13. Neumann U, Berg T, Bahra M, Seehofer D, Langrehr J, Neuhaus R, et al. Fibrosis progression after liver transplantation in patients with recurrent hepatitis C. J Hepatol. 2004; 41:830–836. [PubMed: 15519657]
14. Zekry A, Whiting P, Crawford DH, Angus PW, Jeffrey GP, Padbury RT, et al. Liver transplantation for HCV-associated liver cirrhosis: predictors of outcomes in a population with significant genotype 3 and 4 distribution. Liver Transpl. 2003; 9:339–347. [PubMed: 12682883]
15. Feray C, Gigou M, Samuel D, Paradis V, Mishiro S, Maertens G, et al. Influence of the genotypes of hepatitis C virus on the severity of recurrent liver disease after liver transplantation. Gastroenterology. 1995; 108:1088–1096. [PubMed: 7698576]
16. Shiffman M, Stravitz R, Contos M, Mills A, Sterling R, Luketic V, et al. Histologic recurrence of chronic hepatitis C virus in patients after living donor and deceased donor liver transplantation. Liver Transpl. 2004; 10:1248–1255. [PubMed: 15376308]
17. El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999; 340:745–750. [PubMed: 10072408]
18. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334:693–699. [PubMed: 8594428]
19. Zhou S, Terrault N, Ferrell L, Hahn J, Lau J, Simmonds P, et al. Severity of liver disease in liver transplantation recipients with hepatitis C virus infection: relationship to genotype and level of viremia. Hepatology. 1996; 24:1041–1046. [PubMed: 8903372]
20. Zein N, Rakela J, Poterucha J, Steers J, Wiesner R, Persing D. HCV genotypes in liver transplant recipients: distributionand1-yearfollow-up. LiverTransplantSurg. 1995; 1:354–357.
21. Gordon FD, Poterucha JJ, Germer J, Zein NN, Batts KP, Gross JB Jr, et al. Relationship between hepatitis C genotype and severity of recurrent hepatitis C after liver transplantation. Transplantation. 1997; 63:1419–1423. [PubMed: 9175804]

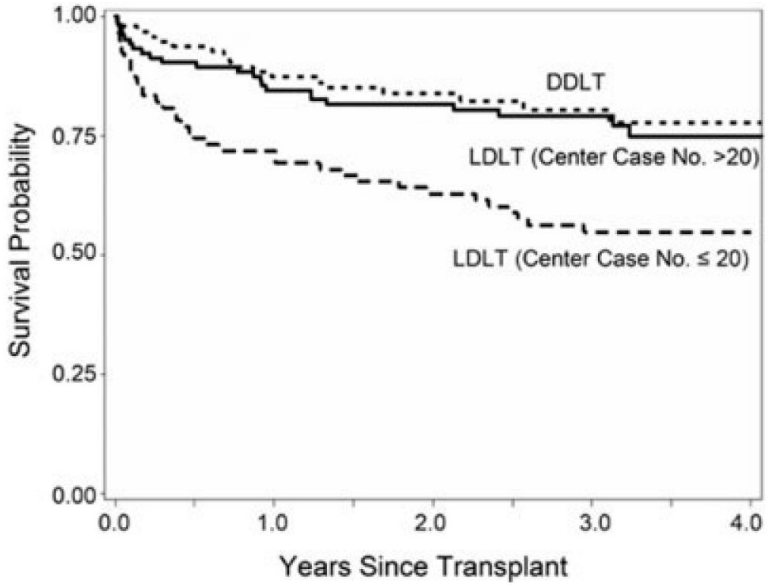

Figure 1.

Graft survival after DDLT (dotted line), LDLT ≤20 (dashed line; first 20 cases at each center), and LDLT >20 (solid line; cases beyond the first 20 at each center). Graft survival was significantly lower in LDLT ≤20 compared to LDLT >20 ($P = 0.0023$) and DDLT ($P = 0.0007$). However, there was no significant difference in graft survival between LDLT >20 and DDLT ($P = 0.66$, log-rank test).

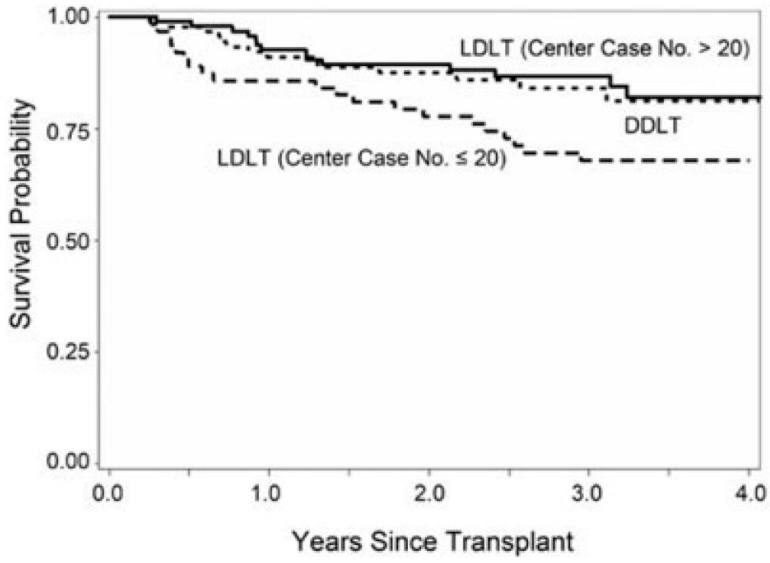

Figure 2.

Graft survival after DDLT (dotted line), LDLT ≤20 (dashed line; first 20 cases at each center), and LDLT >20 (solid line; cases beyond the first 20 at each center) conditioned on graft survival to at least 90 days. Differences in graft survival were seen in LDLT ≤20 compared to LDLT >20 ($P = 0.021$) and DDLT ($P = 0.052$), but there was no significant difference in graft survival between LDLT >20 and DDLT ($P = 0.74$, log-rank test).

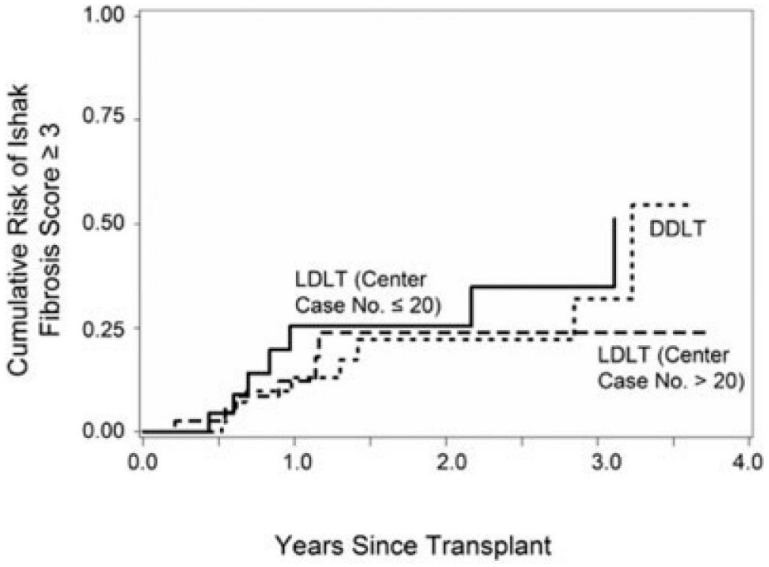

Figure 3.

A total of 123 patients had at least 1 biopsy that occurred ≥30 days posttransplantation and no more than 2 weeks after the start of HCV treatment and had an Ishak fibrosis score. The cumulative risk of Ishak fibrosis score of 3 or more (bridging fibrosis or cirrhosis) on biopsy was not significantly different among LDLT ≤20 (solid line; n = 28), LDLT >20 (dashed line; n = 43), and DDLT (dotted line; n = 52) groups ($P > 0.05$ for all comparisons by log-rank test, unadjusted). Patients were censored at time of treatment of HCV disease.

TABLE 1

Pretransplant and Peritransplant Recipient and Donor Characteristics

	LDLT (n = 181) Median (range) or n (%)	DDLT (n = 94) Median (range) or n (%)	*P* Value*
Recipient age (years)	50.5 (29–71)	52.3 (30–74)	0.17
Male recipients	119 (66)	68 (72)	0.27
Caucasian recipients	166 (92)	84 (89)	0.52
Patients with pre-LT HCC	36 (20)	27 (29)	0.10
Laboratory MELD at transplantation†	14.0 (6–40)	18.0 (7–40)	<0.0001
Donor age (years)	37.7 (19–57)	41.0 (9–72)	0.07
Male donors‡	90 (50)	52 (63)	0.03
Cold ischemia time (minutes)	46.0 (5–480)	399.0 (12–600)	<0.0001

Abbreviation: LT, liver transplant.

*For continuous variables (recipient and donor age, MELD, cold ischemia time), the *P* value is based on a 2-sample *t* test comparing LDLT and DDLT; for dichotomous variables (% male, % Caucasian, % with HCC), the *P* value is based on a chi-square test comparing LDLT and DDLT.

†Range from 6 (lowest risk) to 40 (highest risk).

‡Excludes 11 DDLT with missing donor gender.

TABLE 2

Primary Causes of Graft Loss

	LDLT (n = 34) n (%)	DDLT (n = 6) n (%)
Recurrent HCV	8 (24)	2 (33)
Recurrent HCC	1 (3)	0 (0)
Vascular complications	7 (21)	0 (0)
Primary nonfunction	7 (21)	0 (0)
Infection	3 (9)	2 (33)
Biliary complications	2 (6)	1 (17)
Other	6 (18)	1 (17)

TABLE 3

Predictors of Overall Graft Loss and Graft Loss Beyond First 90 Days*

	Overall Graft Survival		Graft Survival Beyond 90 Days	
Predictor Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
LDLT ≤20 vs. DDLT†	3.04 (1.66, 6.64)	<0.001	2.11 (1.02, 4.37)	0.045
LDLT >20 vs. DDLT†	1.49 (0.77, 2.88)	0.238	1.17 (0.53, 2.54)	0.70
Recipient age (per 10 years)	1.37 (1.01, 1.86)	0.043	1.22 (0.82, 1.80)	0.326
Pre-LT HCC	1.89 (1.08, 3.32)	0.027	2.21 (1.10, 4.42)	0.025
Laboratory MELD at LT (per 5 points)	1.26 (1.07, 1.48)	0.006	1.24 (1.01, 1.54)	0.044
Tacrolimus at baseline	0.71 (0.42, 1.20)	0.201	0.67 (0.34, 1.29)	0.225
Rejection requiring antibody‡	2.36 (1.10, 5.06)	0.028	1.88 (0.72, 4.89)	0.198

Abbreviation: CI, confidence interval.

*Variables tested but not significant ($P > 0.10$) in the multivariable Cox regression model: donor age, cold ischemia time, biliary complications (time-varying covariate) and antiviral treatment (time-varying covariate).

†LDLT ≤20 are those LDLTs performed among the first 20 at a given center. LDLT >20 are those LDLTs performed after at least 20 LDLTs had been performed at the given center.

‡Time-varying covariate.

TABLE 4

Predictors of Overall Patient Death and Patient Death Beyond First 90 Days*

	Overall Patient Survival		Patient Survival Beyond 90 Days	
Predictor Variable	**HR (95% CI)**	***P* Value**	**HR (95% CI)**	***P* Value**
LDLT ≤20 vs. DDLT†	2.66 (1.42, 4.50)	0.002	2.56 (1.25, 5.23)	0.010
LDLT >20 vs. DDLT†	1.34 (0.67, 2.69)	0.404	1.37 (0.63, 2.96)	0.428
Recipient age (per 10 years)	1.37 (0.99, 1.91)	0.058	1.18 (0.81, 1.71)	0.387
Pre-LT HCC	2.24 (1.23, 4.06)	0.008	2.30 (1.19, 4.46)	0.013
Laboratory MELD at LT (per 5 points)	1.30 (1.09, 1.55)	0.003	1.27 (1.04, 1.55)	0.021
Tacrolimus at baseline	0.64 (0.37, 1.10)	0.108	0.76 (0.40, 1.44)	0.399

Abbreviation: CI, confidence interval.

*Variables tested but not significant ($P > 0.10$) in the multivariable Cox regression model: donor age, cold ischemia time, rejection requiring antibody (time-varying covariate), biliary complications (time-varying covariate), and antiviral treatment (time-varying covariate).

†LDLT ≤20 are those LDLTs performed among the first 20 at a given center. LDLT >20 are those LDLTs performed after at least 20 LDLTs had been performed at the given center.

TABLE 5

Liver Disease Severity Evaluated by Liver Biopsy

	LDLT	DDLT	*P*-Value
Duration of histologic follow-up (median, range), months*	12.7 (8.2–32)	13.3 (8.3–52)	0.22
Knodell HAI score at 1 year ± 4 months (median, range)†	3.5 (0–12)	5 (1–12)	0.19
Ishak fibrosis score at 1 year ± 4 months (n, %)†			0.93
0–2	30 (83.3%)	23 (85.2%)	
3–6	5 (13.9%)	3 (11.1%)	

Abbreviation: HAI, hepatitis activity index.

*A total of 138 patients (82 LDLT and 56 DDLT) had at least 1 biopsy.

†Of the 224 patients with a functioning graft at 1 year posttransplantation, 63 (28%; 36 LDLT, 27 DDLT) had liver biopsies available at 1 year ± 4 months that could be evaluated for HCV disease severity. In patients receiving HCV treatment, histology was assessed on the biopsy occurring no more than 2 weeks after start of treatment for HCV. Three DDLT recipients had missing Knodell HAI scores, and 1 LDLT recipient and 1 DDLT recipient had missing Ishak fibrosis score. Knodell HAI score includes necroinflammatory components only (maximum possible score, 18).